83-3 - Rat - Teratogenicity

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DATA EVALUATION REPORT

Study Type: Rat Teratology

TOX. CHEM. No.: 2980

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Test Material: CGA-154281 Technical

Study Number(s): 483-237

Sponsor: CIBA-GEIGY Corp.

Test Facility: Hazleton Laboratories America, Inc.

Title of Report: Rang-Finding Rat Teratology Study with CGA-154281 Technical

Author(s): S. L. Morseth, J.D. Sutherland, and P.L. Burlew

Report Issued: November 14, 1986

Conclusions:

Maternal Toxicity NOEL = 300 mg/kg/day
Maternal Toxicity LEL = 600 mg/kg/day
(increased incidences of abnormal clinical observations; decreased maternal body weight gain)

Embryo/Fetal Toxicity NOEL < 300 mg/kg/day
(decreased fetal weight)

Dose levels tested: 0, 300, 600, 800, and 1000 mg/kg/day

Classification of Data: *Core Guideline*

PC 9115-8

Title of Report: Dose Selection for the Rat Teratology Study with CGA 154281 Technical

Procedure:

1. Five groups of pregnant rats of CRL:CD(SD) BR strain, 7 per group, were treated with 4 concentrations of CGA 154281 suspended in 0.5% carboxymethyl cellulose solution containing 0.1% Tween 80 (300, 600, 800, and 1000 mg/kg/day) by oral intubation daily for 10 consecutive days (initiated on day 6 through day 15 of gestation). The control group received the vehicle solution concurrently with the test compond.

2. The parameters used to determine the maternal and/or embryo/fetal toxicity of CGA 154281 in pregnant rats were body weights, fetal viability and fetal weight in this dose range-finding study.

Methods and Results:

1. Maternal observations for all females were observed daily for mortality and moribundity during the treatment period.

Results: Two females in the high dose group (1000 mg/kg/day) were found dead during the study (one on day 15 of gestation and another one on day 18 of gestation). Remaining animals survived to day 20 of gestation. Alopecia, urine stains, blood crusts on the eyes, nose, and mouth and thin and hunched appearance were observed in all the treated groups. These observations were more frequent and/or more severe in the higher dose groups (600, 800 and 1000 mg/kg/day). (See attached Table 1).

2. Individual body weights were recorded on days 0, 6, 8, 12, 16, and 20 of gestation.

Results: Mean body weights were comparable for all groups on gestation days 0 and 6. During the treatment period (6-15 days of gestation), mean weight loss was observed in the 600, 800, and 1000 mg/kg/day dose groups. In the posttreatment phase of gestation (16-20 days), all groups showed a mean weight gain but the mean weight gains for 800 and 1000 mg/kg/day dose groups were still below the control value. However, both corrected and uncorrected mean body weight changes (0-20) showed a compound-related decrease (See Table 3).

3. Food consumption value was recorded on days 0, 6, 8, 12, 16, and 20 of gestation.

Results: The mean interval food consumption values were lower than control values for all treated groups during the first week of treatment (interval values for days 6-8 and 8-12). During the last part of the treatment (interval values for days 12-16), the mean interval foood consumption values for the treatment groups were greater then control values with the exception of high dose group which was slightly less. (See attached Table 2).

4. Necropsy Observation

All dams that were sacrificed were examined for abnormalities of the thoracic, abdominal or pelvic viscera. The uterus from each pregnant female was excised, weighed, and examined for the number of implantation sites, number of live and

dead fetuses, and the number of early and late resorptions. The ovaries were examined for the number of corpora lutea

A. Gross Pathology:

i. Macroscopic findings in the high dose dams (1000 mg/kg/day) that died prior to scheduled sacrifice included the following: stomach-glandular mucosa with dark red foci or flecks, duodenum congested with white thick creamy material, intestines distended with gas, urinary bladder distended with fluid, adrenals appeared dark red and enlarged, kidney had dilated pelvis, and the liver appeared pale, mottled and/or firm.

ii. Distended cecum was found in the high dose dams at scheduled sacrifice.

iii. None of these macroscopic lesions was observed from that of the corresponding control group.

B. Mean Fetal Data:

	Dose Groups				
	0	300	600	800	1000
No. of females mated	7	7	7	7	7
No. of females pregnant	7	7	7	6	6
Pregnancy rate (%)	100	100	100	85.7*	85.7*
No. of females surviving to day 20	7	7	7	7	5
Suvival Rate (%)	100	100	100	100	71.4*
Mean No. of					
Corpora lutea	14.4	18.0	16.0	15.8	15.8
Implantations	13.4	15.0	14.7	14.2	15.0
Early resorptions	0.9	2.9	2.5	12.7*	11.3*
Late resorptions	0	0.3	0.3	0.2	0.2
Fetuses - lived	12.6	11,9	12.2	1.3*	3.5*
Indices (per litter)					
Mean Implantation Efficiency (%)	93.5	87.3	92.6	89.7.	95.1
Mean Early Resorption Incidence (%)	6.2	18.6	16.7	88.0*	78.0 *
Mean Late Resorption Incidence (%)	0	1.8	2.3	1.2	1.5
Mean Total Resorption Incidence (%)	6.2	20.4	19.0	89.2*	79.4*
Viable fetuses (%)	93.8	79.7	81.1	10.9*	20.6*
No. of Litters with Live fetuses	7	7	6	2*	1*
Mean Fetal Weight	3.4	2.8*	2.5 *	1.7 *	1.8 *

* Noted difference from control value.

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Findings:

i. The pregnancy rate were decreased to 85.7% in the dose groups receiving 800 mg/kg/day or more of CGA 154281 Technical as compared to control value. Survival rate (%) was decreased in the high dose group only (1000 mg/kg/day).

ii. The mean incidence (%) of fetal viability was 93.8, 79.7, 81.1, 10.9, and 20.6 for the 0, 300, 600, 800, and 1000 mg/kg/day dose groups respectively. Fetal viability was clearly affected by the treatment.

iii. The number of litters with live fetuses was decreased in a dose-related manner for the treated groups receiving 800, and 1000 mg/kg/day. The mean fetal body weight values were also decreased in a dose related manner and were lower in all treated groups as compared to that of the control group.

Conclusion:

Maternal Toxicity NOEL = 300 mg/kg/day
Maternal Toxicity LEL = 600 mg/kg/day
(increased incidences of abnormally clinical observations; decreased maternal body weight gain)

Embryo/Fetal Toxicity NOEL 300 mg/kg/day
(decreased fetal weight)

Classification of Data: Core Guideline

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